Treat-and-Extend versus Monthly Regimen in Neovascular Age-Related Macular Degeneration

Results with Ranibizumab from the TREND Study

TREND Study Group

Published in:
Ophthalmology

DOI:
10.1016/j.ophtha.2017.07.014

Publication date:
2018

Document version
Publisher's PDF, also known as Version of record

AMERICAN ACADEMY™ OF OPHTHALMOLOGY

Treat-and-Extend versus Monthly Regimen in Neovascular Age-Related Macular Degeneration

Results with Ranibizumab from the TREND Study

*Rufino Silva, MD, PhD,[1,2,3] András Berta, MD, PhD,[4] Michael Larsen, MD, DMSc,[5] Wayne Macfadden, MD,[6] Chrystel Feller, PhD,[6] Jordi Monés, MD, PhD,[7] on behalf of the TREND Study Group**

Purpose: To evaluate the efficacy and safety of ranibizumab 0.5 mg treat-and-extend (T&E) versus monthly regimens in patients with neovascular age-related macular degeneration (nAMD) from the TReat and extEND (TREND) study.

Design: A 12-month phase 3b visual acuity (VA) assessor-masked, multicenter, randomized, interventional study.

Participants: Six hundred fifty patients.

Methods: Treatment-naïve nAMD patients (age, ≥50 years) were randomized 1:1 to receive either a ranibizumab 0.5 mg T&E (n = 323) or monthly (n = 327) regimen.

Main Outcomes Measures: The primary objective was to show noninferiority of ranibizumab 0.5 mg T&E versus monthly regimen, as assessed by the change in best-corrected VA (BCVA) from baseline to the end of the study. Secondary objectives included change in retinal central subfield thickness (CSFT) from baseline to the end of study, treatment exposure, and safety.

Results: Overall, 89.8% (T&E) and 90.2% (monthly) of patients completed the study. Patient demographic and baseline characteristics were well balanced between the 2 treatment groups. The T&E regimen was noninferior ($P < 0.001$) to the monthly regimen, with a least squares mean BCVA change from baseline of 6.2 versus 8.1 letters to the end of study, respectively. In both treatment groups, most BCVA improvements occurred during the first 6 months and were maintained until the end of the study. The mean change in CSFT from baseline to the end of study was −169.2 μm and −173.3 μm in the T&E and monthly groups, respectively. Fewer injections were required in patients receiving the T&E (8.7) versus monthly (11.1) regimen, with mean number of postbaseline visits of 8.9 and 11.2, respectively. Types and rates of adverse events were comparable between the treatment groups.

Conclusions: Ranibizumab 0.5 mg administered according to a T&E regimen was statistically noninferior and clinically comparable with a monthly regimen in improving VA from baseline to the end of study. No new safety signals for ranibizumab were identified. *Ophthalmology 2018;125:57-65 © 2017 American Academy of Ophthalmology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.aaojournal.org.

Neovascular age-related macular degeneration (nAMD) is one of the major causes of severe vision loss in developed countries, particularly in the population 50 years of age and older.[1,2] Overall, it accounts for 8.7% of total blindness worldwide and for 50% to 60% of new cases of blindness every year.[1–7]

Anti–vascular endothelial growth factors (VEGFs) are considered the first-line therapy for the treatment of patients with nAMD.[8] Ranibizumab 0.5 mg (Lucentis; Novartis Pharma AG, Basel, Switzerland; and Genentech, Inc, South San Francisco, CA) was the first approved anti-VEGF for the treatment of choroidal neovascularization (CNV) secondary to AMD based on the results of 2 phase 3 clinical studies: the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (AMD)[9] and Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration.[10] In these studies, monthly ranibizumab injections resulted in substantial and sustained best-corrected visual acuity (BCVA) improvements over 2 years. However, a monthly treatment regimen may pose the inconvenience of more frequent dosing visits, thus increasing the overall treatment burden for patients.

http://dx.doi.org/10.1016/j.ophtha.2017.07.014
ISSN 0161-6420/17

Consequently, an individualized dosing regimen of ranibizumab, pro re nata (PRN), was evaluated in the Prospective OCT Study with Lucentis for Neovascular AMD,[11] Comparison of AMD Treatments Trials,[12,13] and the Phase III, Double-Masked, Multicenter, Randomized, Active Treatment-Controlled Study of the Efficacy and Safety of 0.5 mg and 2.0 mg Ranibizumab Administered Monthly or on an As-Needed Basis (PRN) in Patients with Subfoveal Neovascular Age-Related Macular Degeneration,[14] in which ranibizumab administered PRN showed an improvement in visual outcomes with fewer injections compared with monthly treatment. However, the burden of monthly monitoring visits remained unaddressed. Furthermore, both monthly and reactive PRN regimens may lead to overtreatment or undertreatment, thus adding to challenges to the management of patients with nAMD.

To minimize both clinic visit and injection frequency, proactive dosing regimens that allow extension of visit intervals, such as treat and extend (T&E),[15] were evaluated. Several studies have evaluated T&E regimens and found the principle to be a feasible option for the treatment of patients with nAMD.[16,17] However, few randomized controlled trials have evaluated the T&E regimen versus a monthly regimen.[18,19] Herein, we report 12-month results of the TREND study, which evaluated the efficacy and safety of a ranibizumab-0.5 mg T&E regimen versus a monthly regimen in patients with nAMD, to assess whether T&E can result in similar visual benefits as observed with the monthly regimen while reducing injection burden for patients, clinicians, and healthcare systems.

Methods

Study Design

The TREND was a 12-month phase 3b visual acuity (VA) assessor-masked, multicenter, interventional study in patients with newly diagnosed nAMD. Monthly treatment has demonstrated maximum visual outcomes in several studies and therefore was selected as a comparator for the T&E dosing regimen in this study. Between December 2013 and November 2015, 650 treatment-naïve patients with visual impairment resulting from active CNV secondary to AMD were enrolled at 90 centers across 18 countries (Table in Appendix 2, available at www.aaojournal.org). The study protocol was reviewed and approved by an independent ethics committee or institutional review board at each center. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from each patient at screening. The study is registered at clinicaltrials.gov with identifier NCT01948830.

Patient Selection

The study population consisted of treatment-naïve patients 50 years of age or older with visual impairment resulting from active CNV secondary to AMD confirmed by presence of active leakage of CNV detected by fluorescein angiography, color fundus photography, or both. Other key inclusion criteria were total area of fibrosis comprising less than 50% of the lesion area and BCVA score between 23 and 78 Early Treatment Diabetic Retinopathy Study (ETDRS) letters at a distance of 4 m (approximately 20/32 and 20/320 Snellen equivalent, respectively).

Patients were excluded if they had any type of advanced, severe, or unstable disease, including any medical condition that can bias assessment or put the patient at special risk; history of stroke or myocardial infarction within 3 months before screening or an uncontrolled systolic blood pressure of more than 160 mmHg or diastolic blood pressure of more than 100 mmHg; prior treatment of the study eye with anti-VEGF or verteporfin photodynamic therapy or corticosteroids within 6 months before screening or intraocular surgery within 3 months before screening; history of focal−grid laser photocoagulation with involvement of the macular area; or uncontrolled glaucoma or atrophy or fibrosis in the study eye (details on the complete inclusion and exclusion criteria are provided in Appendix 3, available at www.aaojournal.org).

Randomization and Treatment

Patients were randomized 1:1 to receive either the ranibizumab 0.5-mg T&E or monthly regimen. Patients in the T&E group received 2 initial monthly ranibizumab injections at baseline (day 1) and month 1. After 1 month, visits in the T&E group were scheduled based on disease activity as assessed by VA and OCT criteria. Patients were treated at monthly intervals until disease activity was resolved, as assessed by spectral-domain OCT according to the investigator's judgment (i.e., no intraretinal or subretinal fluid). If disease activity was not present, the next visit was scheduled in 6 weeks (i.e., the treatment interval, defined as the period between 2 ranibizumab injections, was extended by 2 weeks); however, if disease activity was present, the interval to the next visit was not extended and thus was scheduled in 4 weeks (1 month). The treatment interval could be extended by 2 weeks at each visit as long as there was no disease activity, with a maximum of a 12-week treatment interval. During the course of the study, if disease activity was present, the treatment interval was shortened by 2 weeks, but never to fewer than 4 weeks. The patient was treated at this interval until no disease activity was present, after which an extension of 2 weeks was reactivated. The possibility to extend the interval between treatments was limited to 2 attempts. If disease activity recurred, the visit schedule was shortened by 2 weeks and fixed on this interval up to the end of the study. However, if disease activity was present along with visual impairment, the treatment interval was allowed to shorten by 4 weeks instead of 2 weeks based on the investigator's judgment (Fig 1). In the monthly regimen group, treatment visits were scheduled at monthly intervals up to the end of the study.

Treatment Masking

In this study, the VA assessor who assessed the parameters for the primary end point was masked to the treatment regimen and was not allowed to perform any additional study tasks. The BCVA assessments were performed first before conducting any other assessments and were recorded and archived.

Objectives

The primary objective of the study was to demonstrate noninferiority of the ranibizumab 0.5-mg T&E regimen to the monthly regimen in patients with nAMD as assessed by change in BCVA from baseline to the end of study. For the primary analysis, a noninferiority margin of 5 letters was applied. This was selected based on clinical relevance, because 5 letters constitute 1 line on the ETDRS chart. In the Comparison of AMD Treatments Trials and the Phase III, Double-Masked, Multicenter, Randomized, Active Treatment-Controlled Study of the Efficacy and Safety of 0.5 mg and 2.0 mg Ranibizumab Administered Monthly or on an As-Needed Basis (PRN) in Patients with Subfoveal Neovascular Age-Related Macular Degeneration, noninferiority margins were

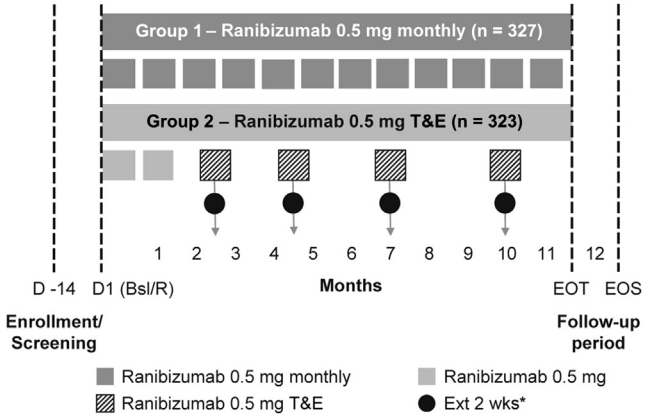


Figure 1. Diagram showing the study design. *Example of possible dosing schedule of a patient with extended visits. Bsl = baseline; D = day; EOS = end of study; EOT = end of treatment; Ext = extension; R = randomization; T&E = treat and extend; wk = week.

4 to 5 letters and were based on a similar rationale regarding clinical relevance for a fewer than 1-line difference.

Secondary objectives included evaluation of the efficacy of ranibizumab 0.5 mg (T&E vs. monthly) as assessed by (1) change in BCVA from baseline to the end of study; (2) average change in BCVA from baseline to month 1 through the end of study; (3) proportion of patients with categorized BCVA gain of 1 letter or more, 5 letters or more, 10 letters or more, 15 letters or more, and 30 letters or more; loss of fewer than 5, fewer than 10, and fewer than 15 letters from baseline to the end of study; and BCVA of 73 letters or more (20/40 Snellen equivalent) over the study period; (4) change in retinal central subfield thickness (CSFT), presence of a fluid-free macula (e.g., no intraretinal or subretinal fluid), and presence of active CNV leakage from baseline to the end of study; (5) treatment frequency and average dosing interval until the end of study; and (6) safety of both dosing regimens of ranibizumab 0.5 mg.

Study Assessments

All efficacy assessments were performed on the study eye. The BCVA was assessed at every visit using the ETDRS VA testing protocol at a starting distance of 4 m. The change in CSFT was assessed at every visit using spectral-domain OCT and was evaluated by a central reading center to determine the status of disease activity. Fluorescein angiography was performed after color fundus photography to assess the choroid and retinal vasculature of the study eye. These assessments were performed by a trained technician at the sites at screening and at the end of study, and the images were evaluated by a central reading center. At all other scheduled visits, the images of the study eye were obtained at the investigator's discretion and were not provided to the reading center. Data on treatment frequency and average dosing interval were collected over the 12-month duration of the study.

Safety assessments included physical examination; vital signs; ophthalmic assessments; and type, frequency, and severity of adverse events (AEs). All ocular AE assessments were performed on both eyes. Intraocular pressure (IOP) was measured at screening and at the end of study in both eyes. In the study eye, pretreatment IOP was assessed at every scheduled visit from day 1, and post-treatment IOP was assessed after each intravitreal ranibizumab injection. If IOP was 25 mmHg or more in the study eye and not transient during the study period, it was treated based on the investigator's discretion. Intravitreal ranibizumab injection was not recommended unless normalization of the IOP was achieved.

Statistical Analysis

The hypothesis testing with respect to noninferiority of BCVA was performed using an analysis of covariance (ANCOVA) model including treatment group as factor and baseline BCVA as continuous variable. The primary analysis was performed on the full analysis set using the last observation carried forward principle for imputing missing BCVA values at the end of the study. The full analysis set comprised all patients to whom a treatment regimen was assigned.

Assuming a standard deviation (SD) of 15 ETDRS letters in the T&E and monthly groups, with a difference of 1.5 in mean change in BCVA from baseline in favor of the monthly regimen, and by applying an ANCOVA model, a sample size of 322 patients per treatment group was considered (to account for loss of information resulting from missing data, the sample size was increased by 10% from 290 to 322). With this sample size, the resulting power for ANCOVA was 80% to establish noninferiority of the T&E regimen versus the monthly regimen at a 1-sided 2.5% level for a non-inferiority margin of 5 letters. The least squares (LS) mean and standard errors for each treatment group and treatment difference along with their 95% confidence intervals were presented. Two-sided *P* values were presented for treatment difference.

The analysis of the secondary efficacy objectives was based on the full analysis set. At all the time points assessed, efficacy variables (BCVA and CSFT) were presented graphically, and descriptive statistics were provided based on absolute values and changes from baseline. Because of the study design, the data from patients randomized to the monthly regimen were recorded at monthly scheduled visits only. In patients randomized to the T&E group, data were recorded on scheduled visits for treatment. These visits were based on a biweekly visit grid; however, each patient had her or his own set of scheduled visits, determined based on disease activity or visual impairment. Data for the patients in the T&E group were mapped to monthly visits.

Changes in BCVA and CSFT from baseline to the end-of-study visit were compared between treatment groups using ANCOVA models (with the baseline covariate) or the *t* test. Categorical variables were presented as the number and percentage of patients in each category. Continuous variables were summarized using descriptive statistics (e.g., number, mean, SD, median, minimum, and maximum). Safety was analyzed using observed data from the safety set that consisted of all patients who received at least 1 application of study treatment and underwent at least 1 post-baseline safety assessment.

Results

Patient Demographic and Baseline Ocular Characteristics

A total of 650 patients were randomized to receive the ranibizumab 0.5 mg T&E (n = 323) or monthly (n = 327) regimen. Overall, 89.8% of patients in the T&E group and 90.2% in the monthly group completed the study. The most frequent reasons for study discontinuation were withdrawal of consent (n = 31) and AEs (n = 11; Fig 2). The safety set included 649 patients (T&E, n = 323; monthly, n = 326).

Patient demographic and baseline ocular characteristics were well balanced between the 2 treatment groups (Table 1). Overall, the mean age of the patients was 75.2 years; 55.4% were women

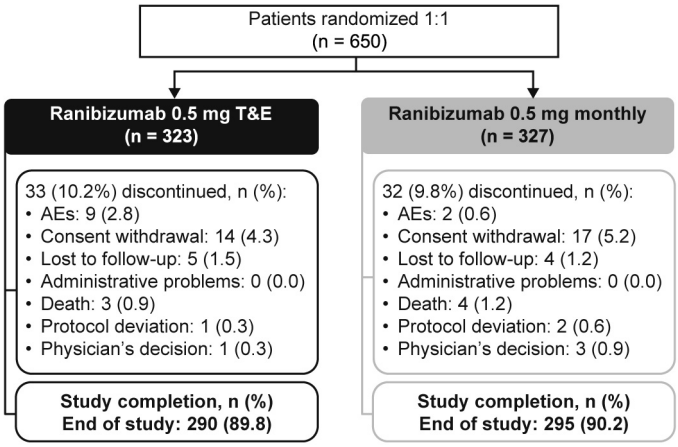


Figure 2. Diagram showing patient disposition (randomized set). Randomized set included all randomized patients to whom a randomization number was assigned. Percentages were based on the total number of patients in the randomized set in the specific treatment group. AEs = adverse events; T&E = treat and extend.

and 91.8% were white. At baseline, the mean BCVA was 60.0 letters, mean IOP was 15.0 mmHg, and mean CSFT was 500.8 μm. The baseline OCT, fluorescein angiography, and color fundus photography characteristics of the study eye were comparable between the 2 treatment groups (Table 1).

Efficacy Outcomes

The LS mean BCVA change from baseline improved by 6.2 ETDRS letters in the T&E group (n = 320) and by 8.1 ETDRS letters in the monthly group (n = 323). The LS mean difference between the treatment groups was −1.9 letters (95% confidence interval, −3.83 to 0.07; $P < 0.001$ for noninferiority). The mean BCVA change from baseline to the end of study increased in the T&E and monthly groups (Fig 3). Patients in both treatment groups achieved a rapid gain in BCVA during the study; most of the improvement occurred during the first 6 months and was maintained until the end of study (Fig 3). The proportion of patients with categorical BCVA gain of 1 letter or more, 5 letters or more, 10 letters or more, 15 letters or more, and 30 letters or more (Fig 4A, available at www.aaojournal.org) and loss of fewer than 5, fewer than 10, and fewer than 15 letters (Fig 4B, available at www.aaojournal.org) and the percentage of patients with BCVA of 73 letters or more from baseline to the end of study (Fig 4C, available at www.aaojournal.org) were similar between the treatment groups.

Anatomic Outcomes

The mean change in CSFT from baseline to the end of study was similar between the groups (T&E, −169.2 μm [n = 291]; monthly, −173.3 μm [n = 287]), with a difference in LS means of 2.9 μm (95% confidence interval, −14.76 to 20.53; $P = 0.748$) between the 2 treatment regimens (Fig 5). From baseline to the end of study, intraretinal cysts and subretinal fluid in the study eye were resolved in 53.4% and 62.3% of patients treated with the ranibizumab T&E regimen versus 49.3% and 60.1% of the patients treated with the monthly regimen, respectively. The proportion of patients with CNV leakage in the study eye at the end of study was comparable between the treatment groups (T&E, 18.7%; monthly, 17.1%). The mean change in CNV leakage area from baseline to the end of study in the study eye treated with the ranibizumab T&E regimen was −1.964 mm^2 (SD, 4.504 mm^2) in 68 patients versus −2.266 mm^2 (SD, 4.860 mm^2) with the monthly regimen in 64 patients.

Treatment Exposure and Visits

The mean number of ranibizumab injections received was 8.7 (SD, 2.68) in the T&E group and 11.1 (SD, 2.43) in the monthly group (Fig 6). In total, 80 patients (24.8%) in the T&E group received 12 injections. However, some of these patients were in the midst of an extended treatment period toward the end of study or their treatment had been extended once and then they returned to monthly injections later. Twenty-three patients received 12 injections of ranibizumab, but were extended to 6 weeks between treatments; therefore, the proportion of patients with 12 monthly injections was 17.6% (i.e., [80 − 23]/323 = 57/323). A large proportion of patients (61.9%) treated with the T&E regimen had a maximum treatment interval of 8 weeks or more (Fig 7). The mean number of postbaseline visits was 8.9 (SD, 2.56) for the T&E regimen and 11.2 (SD, 2.37) for the monthly regimen, with an average mean time between 2 consecutive visits of 40.1 days for the T&E regimen and 28.5 days for the monthly regimen.

Safety Outcomes

Overall, 36.4% and 47.9% of the patients reported ocular AEs in the study eye and nonocular AEs, respectively. The most common ocular AEs reported in both treatment groups were IOP increased (T&E, 8.4%; monthly, 8.6%), followed by conjunctival hemorrhage (T&E, 4.3%; monthly, 5.8%). Reduced VA was reported in 4.6% of the patients in the T&E group versus 3.7% in the monthly group (Table 2). The most common nonocular AEs reported in both treatment groups were nasopharyngitis (T&E, 5.6%; monthly, 8.0%), hypertension (T&E, 7.1%; monthly, 4.0%), influenza (T&E, 2.8%; monthly, 3.7%), and bronchitis (T&E, 2.5%; monthly, 3.7%; Table 2).

Overall, ocular serious adverse events (SAEs) in the study eye were similar between the treatment groups (1.2% each). There were only single reports of any ocular SAE of the study eye. Endophthalmitis was reported in 1 patient (0.3%) in the monthly group (Table 3). Overall, nonocular SAEs were reported in 11.4% of patients (T&E, 11.1%; monthly, 11.7%). Five patients in the T&E group (drug ineffective, n = 2 [0.6%]; blindness, headache, nAMD, retinal hemorrhage, and subretinal fluid, n = 1 each

Table 1. Patient Demographic and Baseline Ocular Characteristics (Randomized Set)

Characteristics	Ranibizumab 0.5 mg Treat and Extend (n = 323)*	Ranibizumab 0.5 mg Monthly (n = 327)*
Age (yrs), mean (SD)	75.3 (8.61)	75.2 (8.13)
Female gender (%)	55.4	55.4
White race (%)	91.6	92.0
VA (ETDRS letters), mean (SD)	59.5 (13.21)	60.6 (13.92)
CSFT (μm), mean (SD)	504.0 (189.94)	497.7 (187.23)
IOP (mmHg), mean (SD)	14.9 (2.66)	15.1 (2.91)
Macular edema, no. (%)		
Absent	52 (16.1)	51 (15.6)
Definite	269 (83.3)	275 (84.1)
Cannot grade	1 (0.3)	0 (0.0)
Missing	1 (0.3)	1 (0.3)
Presence of subretinal fluid, no. (%)		
Yes	288 (89.2)	293 (89.6)
No	34 (10.5)	33 (10.1)
Cannot grade	0 (0.0)	0 (0.0)
Missing	1 (0.3)	1 (0.3)
Presence of cyst, no. (%)		
Yes	180 (55.7)	161 (49.2)
No	142 (44.0)	165 (50.5)
Cannot grade	0 (0.0)	0 (0.0)
Missing	1 (0.3)	1 (0.3)
Area of lesion (mm^2), mean (SD)	6.5 (5.72)	6.2 (5.30)
Total area of leakage (mm^2), mean (SD)	5.9 (5.23)	5.6 (4.66)
Area of CNV (mm^2), mean (SD)	1.9 (2.29)	1.7 (1.74)
CNV secondary, no. (%)		
AMD	310 (96.0)	316 (96.6)
Presence of fluorescein leakage, no. (%)		
Yes	256 (79.3)	260 (79.5)
No	53 (16.4)	52 (15.9)
Cannot grade	1 (0.3)	3 (0.9)
Not applicable	11 (3.4)	10 (3.1)
Missing	2 (0.6)	2 (0.6)
Presence of hemorrhage, no. (%)		
Yes	168 (52.0)	147 (45.0)
No	153 (47.4)	176 (53.8)
Cannot grade	0 (0.0)	2 (0.6)
Missing	2 (0.6)	2 (0.6)
Type of lesion, no. (%)		
100% classic	86 (26.6)	88 (26.9)
Predominantly classic	27 (8.4)	23 (7.0)
Minimally classic	33 (10.2)	11 (3.4)
Occult with no classic component	138 (42.7)	171 (52.3)
Cannot grade	17 (5.3)	13 (4.0)
Other	9 (2.8)	10 (3.1)
Not applicable	11 (3.4)	9 (2.8)
Missing	2 (0.6)	2 (0.6)

AMD = age-related macular degeneration; CNV = choroidal neovascularization; CSFT = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = intraocular pressure; SD = standard deviation; VA = visual acuity.
Randomized set included all randomized patients to whom a randomization number was assigned. Percentages were based on the total number of patients in the randomized set in the specific treatment group.
*Number of patients at enrollment.

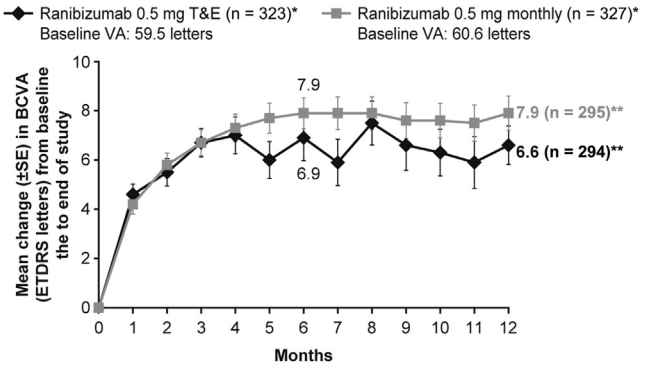


Figure 3. Graph showing the mean change in best-corrected visual acuity (BCVA) from baseline to the end of study (full analysis set). Full analysis set included all patients to whom treatment regimen was assigned. Note that patients in the treat-and-extend (T&E) group were not seen at fixed intervals after the second visit. The monthly BCVA values shown in the graph are nominal sliding averages derived by the following rule: for a given month, the nearest value within ±2 weeks was used. If there were 2 values within that period, the mean was used. End of study refers to month 12 for patients randomized to the monthly arm and to the last scheduled visit (either month 12 or month 12.5) for patients who were randomized to the T&E arm. *Number of patients in the full analysis set. **Number of patients evaluated at baseline and month 12. ETDRS = Early Treatment Diabetic Retinopathy Study; SE = standard error; VA = visual acuity.

[0.3% each]), and 3 patients in the monthly group (drug ineffective, n = 2 [0.6%]; macular hole, n = 1 [0.3%]) discontinued the study drug because of ocular AEs, whereas 1 patient in each treatment group (T&E: retinal hemorrhage, n = 1 [0.3%]; monthly: macular hole, n = 1 [0.3%]) discontinued the study drug because of ocular SAEs. The number of deaths was similar between the 2

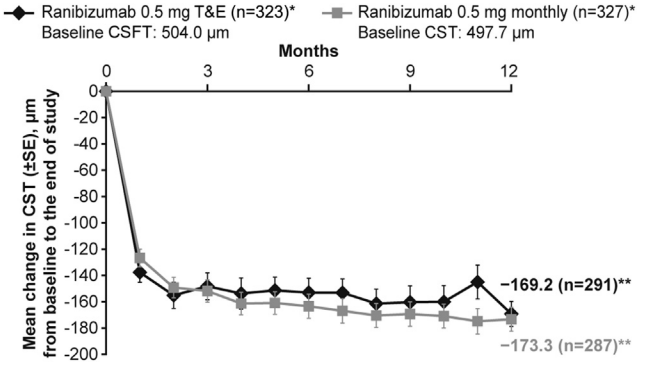
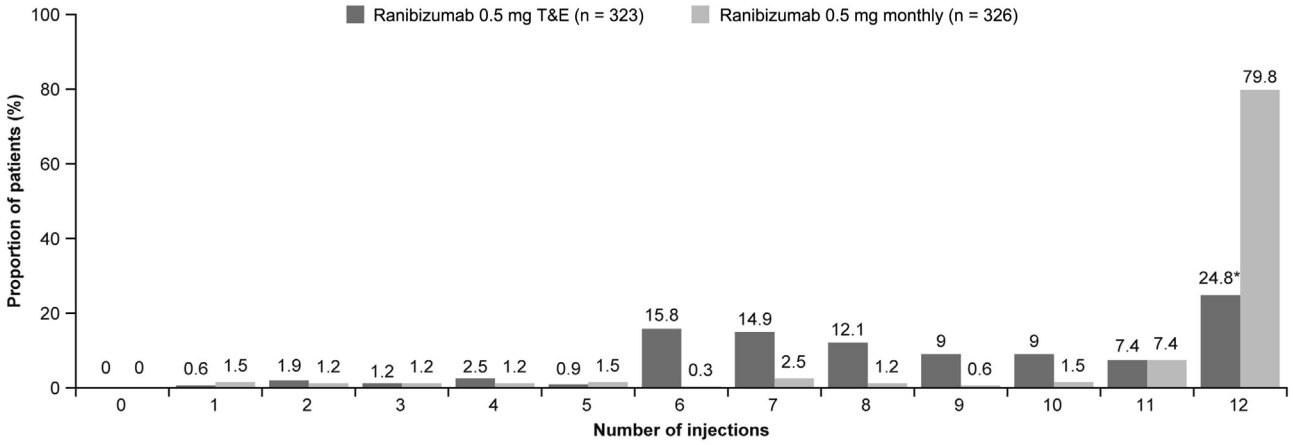


Figure 5. Graph showing the mean change in central subfield thickness (CSFT) from baseline to the end of study (full analysis set). Full analysis set included all patients to whom treatment regimen was assigned. Note that patients in the treat-and-extend (T&E) group were not seen at fixed intervals after the second visit. The monthly CSFT values shown in the graph are nominal sliding averages derived by the following rule: for a given month, the nearest value within ±2 weeks was used. If there were 2 values within that period, the mean was used. End of study refers to month 12 for patients randomized to the monthly arm and to the last scheduled visit (either month 12 or month 12.5) for patients who were randomized to the T&E arm. *Number of patients in the full analysis set. **Number of patients evaluated both at baseline and the end of study (full analysis set).



Number of injections	Ranibizumab 0.5 mg T&E (n = 323)	Ranibizumab 0.5 mg monthly (n = 326)
Total	2802	3612
Mean (SD)	8.7 (2.68)	11.1 (2.43)

Figure 6. Bar graph showing the proportion of patients receiving a given number of ranibizumab injections in the study eye during the 1-year study, shown for each treatment group: treat and extend (T&E) and monthly (safety set). In the T&E group, approximately 60% of the patients received 6 to 10 injections. Safety set consisted of all patients who received at least 1 application of study treatment and had at least 1 postbaseline safety assessment. Percentages are based on the number of patients in the safety set in the specific treatment group. *Includes 23 patients who received 12 injections, but were extended to 6 weeks; therefore the percentage of patients with 12 injections was 80 − 23/323 patients = 57 [17.65%]. SD = standard deviation.

treatment groups (3 deaths in the T&E group and 4 deaths in the monthly group). No deaths were suspected by the investigator to be related to the study treatment. In summary, the incidence of ocular and nonocular AEs and SAEs and deaths was similar, and no new safety signals were observed in either of the 2 treatment groups.

Discussion

The TREND study is one of the largest randomized clinical trials in patients with nAMD to evaluate the efficacy of the T&E dosing regimen versus monthly therapy. Ranibizumab 0.5 mg administered according to a T&E dosing regimen was noninferior ($P < 0.001$) and clinically comparable with a monthly regimen in improving VA from baseline to the end of study. The LS mean BCVA change from baseline to the end of study was 6.2 letters in the T&E group and 8.1 letters in the monthly group. Patients in both treatment groups achieved a similar and rapid gain in BCVA during the study, with most of the improvement occurring during the first 6 months and generally maintained until the end of study. These functional outcomes were supported further by the corresponding anatomic improvements. These comparable results were achieved with approximately 2.5 fewer mean ranibizumab injections in the T&E group than the monthly group (8.7 vs. 11.1) and with a reduced mean number of corresponding visits (8.9 vs. 11.2). The average duration between the visits was 40.1 days in the T&E group and 28.5 days in the monthly group. In the T&E group, 51.7% of the patients received 6 to 9 injections. These gains in VA with the ranibizumab T&E regimen in TREND were comparable with those observed with the monthly regimen in the pivotal Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration, but with fewer clinic visits and injections over 12 months.[10]

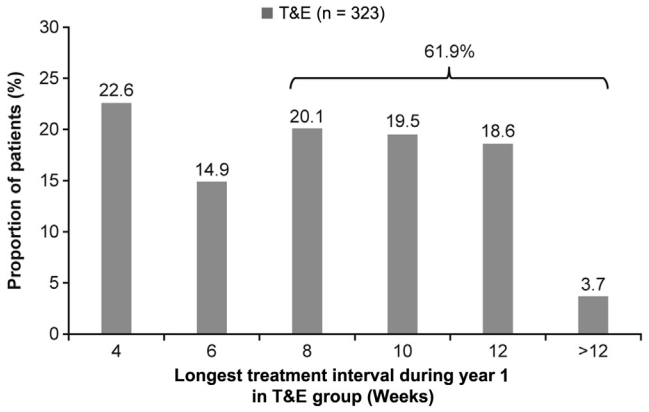


Figure 7. Bar graph showing the longest intravitreal injection treatment interval achieved during 1 year of ranibizumab treat-and-extend (T&E) regimen (full analysis set). The longest possible interval, per protocol, was 12 weeks. Full analysis set included all patients to whom treatment regimen was assigned.

Previous studies have suggested that a large proportion of patients with nAMD maintain VA gains with individualized PRN treatment regimens.[12,13,16–20] However, monthly monitoring is not always required for successful treatment. Variations in retreatment requirements of patients indicate that monthly or frequent monitoring may not be necessary. The T&E regimen considers these varying patient requirements, thus allowing for a tailored follow-up schedule.

Several retrospective and prospective studies have shown that the ranibizumab T&E regimen provides sustained improvements in VA with an average of 9.6 letters in an average of 8.1 injections in the first year of treatment, thus

Table 2. Proportion of Patients with Ocular and Nonocular Adverse Events Regardless of Study Drug Relationship (≥2% in Any Group) and by Preferred Term (Safety Set)

Preferred Term	Ranibizumab 0.5 mg Treat and Extend (n = 323)	Ranibizumab 0.5 mg Monthly (n = 326)
Ocular AEs, total	**116 (35.9)**	**120 (36.8)**
IOP increased	27 (8.4)	28 (8.6)
Conjunctival hemorrhage	14 (4.3)	19 (5.8)
Visual acuity reduced	15 (4.6)	12 (3.7)
Conjunctivitis	10 (3.1)	6 (1.8)
Eye pain	10 (3.1)	5 (1.5)
Cataract	7 (2.2)	7 (2.1)
Retinal hemorrhage	6 (1.9)	8 (2.5)
Dry eye	6 (1.9)	7 (2.1)
Nonocular AEs, total	**150 (46.4)**	**161 (49.4)**
Nasopharyngitis	18 (5.6)	26 (8.0)
Hypertension	23 (7.1)	13 (4.0)
Influenza	9 (2.8)	12 (3.7)
Bronchitis	8 (2.5)	12 (3.7)
Pneumonia	7 (2.2)	5 (1.5)

AE = adverse event; IOP = intraocular pressure.
Data are no. (%). Safety set included all patients who underwent at least 1 application of study treatment and had at least 1 postbaseline safety assessment. A patient with multiple incidences of an AE having undergone 1 treatment was counted only once in the AE category. Adverse events with a start date on or after the date of first administration of study treatment in the study eye were counted.
Boldface values indicate total safety events.

Table 3. Proportion of Patients (%) with Ocular (≥1 Patients in Any Group) and Nonocular (≥2 Patients in Any Group) Serious Adverse Events Regardless of Study Drug Relationship, by Preferred Term (Safety Set)

Preferred Term	Ranibizumab 0.5 mg Treat and Extend (n = 323)	Ranibizumab 0.5 mg Monthly (n = 326)
Ocular SAEs, total	**4 (1.2)**	**4 (1.2)**
Corneal erosion	1 (0.3)	0 (0.0)
Corneal infiltrates	1 (0.3)	0 (0.0)
Dacryostenosis acquired	0 (0.0)	1 (0.3)
Endophthalmitis	0 (0.0)	1 (0.3)
IOP increased	0 (0.0)	1 (0.3)
Macular hole	0 (0.0)	1 (0.3)
Retinal detachment	1 (0.3)	0 (0.0)
Retinal hemorrhage	1 (0.3)	0 (0.0)
Retinal tear	1 (0.3)	0 (0.0)
Vitreous hemorrhage	1 (0.3)	0 (0.0)
Nonocular SAEs, total	**36 (11.1)**	**38 (11.7)**
Pneumonia	4 (1.2)	2 (0.6)
Transient ischemic attack	3 (0.9)	1 (0.3)
Chronic obstructive pulmonary disease	2 (0.6)	1 (0.3)
Dyspnea	2 (0.6)	1 (0.3)
Bronchitis	2 (0.6)	0 (0.0)
Cerebrovascular accident	0 (0.0)	2 (0.6)
Femur fracture	2 (0.6)	0 (0.0)
Hypotension	2 (0.6)	0 (0.0)
Lung neoplasm malignant	0 (0.0)	2 (0.6)
Myocardial infarction	2 (0.6)	0 (0.0)
Sciatica	0 (0.0)	2 (0.6)
Vertigo	2 (0.6)	0 (0.0)
Death	**3 (0.9)**	**4 (1.2)**

IOP = intraocular pressure; SAE = serious adverse event.
Data are no. (%). Safety set included all patients who underwent at least 1 application of study treatment and had at least 1 postbaseline safety assessment. A patient with multiple occurrences of an SAE having undergone 1 treatment was counted only once in the SAE category. Serious adverse events with start date on or after the date of first administration of study treatment in the study eye were counted.
Boldface values indicate total safety events.

optimizing injection and monitoring frequencies.[1,17–25] These outcomes also were observed to be comparable with the large, real-world observational studies conducted in patients with nAMD.[26,27] The results from the TREND study with the ranibizumab T&E regimen were comparable with those observed by Toalster et al[17] and in the Lucentis Compared to Avastin Study,[18] in which the mean increase in BCVA was 7.0 letters and 8.2 letters, respectively, with a mean of 8 ranibizumab injections each over 12 months. Similarly, the proportion of patients with 15 letters or more of VA gain (25.8%) in the T&E group was comparable with that observed in the Lucentis Compared to Avastin Study (26.7%)[18] and the study by Gupta et al[16] (32.0%). When comparing the TREND results with another randomized clinical study (TREX) which also compared a monthly regimen with a T&E regimen, similar BCVA gains were observed with a monthly regimen in both studies (TREND, 8.1 letters; TREX, 9.2 letters), although average gains were higher with the T&E regimen in the TREX study (TREND, 6.2 letters; TREX, 10.5 letters).[19] However, these data should be interpreted with caution considering the obvious limitations of cross-trial comparisons.

A similar proportion of patients in the 2 treatment groups in the TREND study reported ocular AEs (36.4% overall) and nonocular AEs (47.9% overall) in the study eye. During the study, 3 deaths were reported in the T&E group and 4 were reported in the monthly group; however, none were suspected to be related to the study medication by the investigator. Over the course of the study, the incidence of ocular SAEs (1.2% in each treatment group) and nonocular SAEs (11.1% in the T&E group and 11.7% in the monthly group) were similar. Overall, the safety findings were consistent with the well-established safety profile of ranibizumab.[28]

This study was limited by a follow-up period of 12 months. Further reduction on treatment burden may have been shown in a longer study period. Despite this limitation, the study met its primary end point by demonstrating similar efficacy with fewer injections and visits in patients treated with the T&E regimen. In addition, the adequate sample size of patients included in this study adds to the evidence base of the existing literature supporting T&E as an important alternative option to monthly ranibizumab treatment.[13,17–20] Specifically, the titrated, individualized extension of visit intervals during the first year of a T&E regimen may provide valuable input for case management with a minimized treatment burden in subsequent years.

It is well established that good results can be obtained with the PRN regimen in a controlled clinical study.[11–14]

However, in a real-world clinical setting, improvement and maintenance of these gains often is lower because of a reduced number of retreatments.[29] Data from uncontrolled, retrospective analyses have shown that the PRN regimen leading to fewer than 5 injections in the first year are insufficient to sustain VA improvements.[30–32] These findings emphasize the need for more aggressive treatment with a higher frequency of treatment regimens or with stringent retreatment criteria within PRN regimens to avoid undertreatment or irreversible loss of vision. In contrast, based on clinical reports, a proactive T&E regimen has been shown to provide better functional outcomes than a PRN regimen with fewer treatment visits and with a mean of approximately 6 to 8 injections during the first year of treatment.[18,23,33,34]

To summarize, ranibizumab 0.5 mg administered according to a T&E regimen was statistically noninferior and clinically comparable with a ranibizumab monthly regimen in improving VA from baseline to the end of study in patients with nAMD. Patients in both treatment groups achieved a rapid initial gain in BCVA, which was maintained up to the end of study. No new safety signals were identified with ranibizumab treatment during the study. Ranibizumab is the first licensed anti-VEGF therapy with a label that allows customized or individualized dosing treatment approach of T&E from the first year. The T&E approach may be a viable option for patients, allowing maintenance of visual gains with less than monthly monitoring. It offers opportunities to individualize patient management while minimizing treatment burden and costs associated with patient care.[33]

Acknowledgments. The authors thank Rhutika Desai and Urvashi Bawane (Scientific Services Practice - Product Lifecycle Services, Novartis Healthcare Pvt. Ltd, Hyderabad, India) for medical writing and editorial assistance towards development of this article.

References

1. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year. 2002. *Bull World Health Org*. 2004;82:844-851.
2. Eye Diseases Prevalence Research Group. Causes and prevalence of visual impairment among adults in the United States. *Arch Ophthalmol*. 2004;122:477-485.
3. Mitchell P, Smith W, Attebo K, Wang JJ. Prevalence of age-related maculopathy in Australia. The Blue Mountains Eye Study. *Ophthalmology*. 1995;102:1450-1460.
4. Klaver CC, Assink JJ, van Leeuwen R, et al. Incidence and progression rates of age-related maculopathy: the Rotterdam Study. *Invest Ophthalmol Vis Sci*. 2001;42:2237-2241.
5. Kawasaki R, Yasuda M, Song SJ, et al. The prevalence of age-related macular degeneration in Asians: a systematic review and meta-analysis. *Ophthalmology*. 2010;117:921-927.
6. Wong TY, Chakravarthy U, Klein R, et al. The natural history and prognosis of neovascular age-related macular degeneration: a systematic review of the literature and meta-analysis. *Ophthalmology*. 2008;115:116-126.
7. Cachulo Mda L, Lains I, Lobo C, et al. Age-related macular degeneration in Portugal: prevalence and risk factors in a coastal and an inland town. The Coimbra Eye Study—report 2. *Acta Ophthalmol*. 2016;94(6):e442-e453.
8. Solomon SD, Lindsley K, Vedula SS, et al. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. *Cochrane Database Syst Rev*. 2014;8:1-55.
9. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1419-1431.
10. Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR study. *Ophthalmology*. 2009;116:57-65.e5.
11. Lalwani GA, Rosenfeld PJ, Fung AE, et al. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. *Am J Ophthalmol*. 2009;148(1):43-58.e1.
12. CATT Research Group; Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology*. 2012;119:1388-1398.
13. CATT Research Group; Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011;364:1897-1908.
14. Ho AC, Busbee BG, Regillo CD, et al. Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology*. 2014;121:2181-2192.
15. Spaide RF. Ranibizumab according to need: a treatment for age-related macular degeneration. *Am J Ophthalmol*. 2007;143:679-680.
16. Gupta OP, Shienbaum G, Patel AH, et al. A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration clinical and economic impact. *Ophthalmology*. 2010;117:2134-2140.
17. Toalster N, Russell M, Ng P. A 12-month prospective trial of inject and extend regimen for ranibizumab treatment of age-related macular degeneration. *Retina*. 2013;33:1351-1358.
18. Berg K, Pedersen TR, Sandvik L, Bragadóttir R. Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol. *Ophthalmology*. 2015;122:146-152.
19. Wykoff CC, Croft DE, Brown DM, et al. Prospective trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration: TREX-AMD 1-year results. *Ophthalmology*. 2015;122:2514-2522.
20. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. *Am J Ophthalmol*. 2008;145:239-248.
21. Schmidt-Erfurth U, Eldem B, Guymer R, et al. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. *Ophthalmology*. 2011;118:831-839.
22. Abedi F, Wickremasinghe S, Islam AF, et al. Anti-VEGF treatment in neovascular age-related macular degeneration: a treat-and-extend protocol over 2 years. *Retina*. 2014;34:1531-1538.
23. Oubraham H, Cohen SY, Samimi S, et al. Inject and extend dosing versus dosing as needed: a comparative retrospective study of ranibizumab in exudative age-related macular degeneration. *Retina*. 2011;31:26-30.
24. Calvo P, Wang, Ferreras A, et al. Treat and extend versus treat and observe regimens in wet age-related macular degeneration patients treated with ranibizumab: 3-year surveillance period. *J Clin Exp Ophthalmol*. 2014;5:1-5.

25. Gianniou C, Dirani A, Ferrini W, et al. Two-year outcome of an observe-and-plan regimen for neovascular age-related macular degeneration: how to alleviate the clinical burden with maintained functional results. *Eye*. 2015;29:450-451.
26. Gillies MC, Walton RJ, Arnold JJ, et al. Comparison of outcomes from a phase 3 study of age-related macular degeneration with a matched, observational cohort. *Ophthalmology*. 2014;121:676-681.
27. Arnold JJ, Campain A, Barthelmes D, et al. Two-year outcomes of "treat and extend" intravitreal therapy for neovascular age-related macular degeneration. *Ophthalmology*. 2015;122:1212-1219.
28. Silva R, Axer-Siegel R, Eldem B, et al. The SECURE study: long-term safety of ranibizumab 0.5 mg in neovascular age-related macular degeneration. *Ophthalmology*. 2013;120(1):130-139.
29. Holz FG, Amoaku W, Donate J, et al. Safety and efficacy of a flexible dosing regimen of ranibizumab in neovascular age-related macular degeneration: the SUSTAIN study. *Ophthalmology*. 2011;118:663-671.
30. Cohen SY, Dubois L, Tadayoni R, et al. Results of one year's treatment with ranibizumab for exudative age-related macular degeneration in a clinical setting. *Am J Ophthalmol*. 2009;148:409-413.
31. Dadgostar H, Ventura AA, Chung JY, et al. Evaluation of injection frequency and visual acuity outcomes for ranibizumab monotherapy in exudative age-related macular degeneration. *Ophthalmology*. 2009;116:1740-1747.
32. Wolf A, Kampik A. Efficacy of treatment with ranibizumab in patients with wet age-related macular degeneration in routine clinical care: data from the COMPASS health services research. *Graefes Arch Clin Exp Ophthalmol*. 2014;252:647-655.
33. Chen YN, Powell AM, Mao A, Sheidow TG. Retrospective review of Lucentis "treat and extend" patterns and outcomes in age-related macular degeneration. *Retina*. 2016;36:272-278.
34. Stewart M. Individualized treatment of neovascular age-related macular degeneration: what are patients gaining? Or losing? *J Clin Med*. 2015;4(5):1079-1101.

Footnotes and Financial Disclosures

Originally received: April 5, 2017.
Final revision: June 28, 2017.
Accepted: July 14, 2017.
Available online: September 8, 2017. Manuscript no. 2017-688.

[1] Department of Ophthalmology, Centro Hospitalar e Universitário de Coimbra (CHUC), Coimbra, Portugal.

[2] Institute for Biomedical Imaging and Life Sciences, Faculty of Medicine, University of Coimbra (IBILI-FMUC), Portugal.

[3] Association for Innovation and Biomedical Research on Light and Image (AIBILI), Coimbra, Portugal.

[4] Department of Ophthalmology, Faculty of Medicine, Medical and Health Science Center, University of Debrecen, Debrecen, Hungary.

[5] Department of Ophthalmology, Rigshospitalet and Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

[6] Novartis Pharma AG, Basel, Switzerland.

[7] Institut de la Macula, Barcelona, Spain; Barcelona Macula Foundation, Barcelona, Spain.

Presented at: 32nd Asia Pacific Academy of Ophthalmology (APAO) Congress, March 2017, Singapore, Republic of Singapore; and Association for Research in Vision and Ophthalmology-Asia Congress, February 2017, Brisbane, Australia.

*A complete listing of the members of the TREND Study Group is available in Appendix 1 (available at www.aaojournal.org).

Financial Disclosure(s):
The author(s) have made the following disclosure(s): R.S.: Consultant — Allergan, Alimera, Alcon, Bayer, Novartis, THEA; Financial support — Bayer, Alimera, Angelini, THEA, Allergan, Novartis

M.L.: Consultant, Lecturer, Financial support (to institution) — Novartis, Allergan, Alcon, Roche

W.M.: Employee — Novartis Pharma AG (Basel, Switzerland)

C.F.: Employee — Novartis Pharma AG (Basel, Switzerland)

J.M.: Consultant — Novartis, Allergan, Bayer, Alcon, Ophthotech, Notal Vision, Alimera, Genentech; Financial support — Novartis, Bayer, Alcon, Ophthotech, Roche; Lecturer — Novartis, Allergan, Ophthotech

This study was funded and managed by Novartis Pharma AG, Basel, Switzerland.

Author Contributions:

Conception and design: Silva, Berta, Larsen, Monés

Analysis and interpretation: Silva, Berta, Larsen, Macfadden, Feller, Monés

Data collection: Silva, Berta, Larsen, Macfadden, Feller, Monés

Obtained funding: none

Overall responsibility: Silva, Berta, Larsen, Macfadden, Feller, Monés

Abbreviations and Acronyms:
AE = adverse event; **AMD** = age-related macular degeneration; **ANCOVA** = analysis of covariance; **BCVA** = best-corrected visual acuity; **CNV** = choroidal neovascularization; **CSFT** = central subfield thickness; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **IOP** = intraocular pressure; **LS** = least squares; **nAMD** = neovascular age-related macular degeneration; **PRN** = pro re nata; **SAE** = serious adverse event; **SD** = standard deviation; **T&E** = treat and extend; **TREND** = TReat and extEND; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

Correspondence:
Rufino Silva, MD, PhD, Department of Ophthalmology, Centro Hospitalar e Universitário de Coimbra, Praceta Prof. Mota Pinto, 3000-075 Coimbra, Portugal. E-mail: rufino.silva@oftalmologia.co.pt.